Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment

Vincent Cogliano, Yann Grosse, Robert Baan, Kurt Straif, Béatrice Secretan, and Fatiha El Ghissassi
WHO International Agency for Research on Cancer

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In June, 2005, 21 scientists from eight countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to assess the carcinogenicity of combined (oestrogen-progestagen) contraceptives and hormone therapy to humans. Their assessment will be reported as volume 91 of the IARC Monographs,[1] updating previous assessments of these agents.[2]

Worldwide, more than 100 million women—about 10% of all women of reproductive age—use combined contraceptives. Use varies substantially between countries, but is generally higher in more-developed countries (16%) than in less-developed (6%) countries. Rates of ever-use are much higher than are those of present users, exceeding 80% in some more-developed countries and amounting to about 300 million women worldwide. Overall, use of combined contraception is rising.

Most combined contraceptives are taken orally, but they can also be delivered by injection, transdermal patch, or vaginal ring. Both oestrogenic and progestagenic components are readily absorbed and undergo metabolic transformation, especially in the liver. This first-pass effect reduces the overall bioavailability of oral contraceptives and increases the dose to the liver. Formulations of combined contraceptives continue to evolve, trending towards lower-dose oestrogens and new, less androgenic progestagens.

Many epidemiological studies have investigated associations between the use of combined oral contraceptives and development of cancer at various sites. For breast cancer, more than ten cohort studies and 60 case-control studies, including more than 60 000 women are available. Overall, the relative risk of developing breast cancer is slightly increased in present users and recent users compared with never users. 10 years after cessation of use, the risk seems to be similar to that in never users. Biopsy samples obtained during randomised trials showed that use of combined contraceptives increases the proliferation of human breast epithelial cells.

The risk of cervical cancer increases with duration of use of combined oral contraceptives. Studies that investigated human papillomavirus infection (found in almost all cases of cervical cancer[3]) suggest that the prevalence of infection is not increased in women who use combined contraceptives, and increased risk of cervical cancer was recorded in analyses of data from those who were positive for human papillomavirus. Data from in-vitro studies and animal studies suggest that oestrogens and progestagens could enhance expression of certain human-papillomavirus genes and stimulate cell proliferation in the human cervix through hormone-response elements in the viral genome and through receptor-mediated mechanisms, although other mechanisms could also be involved.

The risk of hepatocellular carcinoma is heightened in long-term users of combined oral contraceptives in populations with low frequencies of hepatitis-B infection and chronic liver disease, two of the main causes of human liver cancer. Increases in the occurrence of hepatocellular carcinoma were also noted in analyses that excluded women with such infections. Three case-control studies in populations with a high frequency of hepatitis infection reported no significant rise, but few data were available on long-term use. This suggests that risks of liver cancer from the use of combined contraceptives in conjunction with a hepatitis infection are not multiplicative.

Data from studies in animals lend support to these findings of heightened cancer risk. Several oestrogen-progestagen combinations induce tumours at several sites in rats and mice. Oestrogens or progestagens given alone also induce carcinogenic effects. There is evidence that some oestrogens have a direct genotoxic effect and this might also be the case for some progestagens.

By sharp contrast, the risk of endometrial cancer is consistently reduced in women who used combined oral contraceptives. The reduction is generally greater with longer duration of use, and some reduction persists at least 15 years after cessation of use. Few data are available, however, on low-dose formulations. Mechanistic data lend support to a reduction in risk, showing atrophic and antiproliferative effects in the endometrium.

The risk of ovarian cancer is also reduced in women who used combined oral contraceptives. The reduction is generally greater with longer duration of use, and a reduced risk persists for at least 20 years after cessation of use. Mechanistic data lend support to a reduction in risk: one combination of oestrogen and progestagen has been shown to induce apoptosis of ovarian epithelial cells in monkeys.

Several studies have investigated an association between combined oral contraceptives and colorectal

IARC Monograph Working Group
C La Vecchia—Chair (Italy); P Autier (Belgium); G Rosano (Italy); R Stafford (New Zealand); L Vatten (Norway); S Shapiro (South Africa); E Fernández (Spain); V Beral, J Peto (UK); G Anderson, M Bosland, S Haslam, T Junghans, D Kaufman, A Molinolo, S Olin, P Newcomb, F Parl, D Roy, F Stanczyk (unable to attend), D Thomas (USA)

cancer. The evidence suggests that combined oral contraceptives do not increase the risk of colorectal cancer. Mechanistic studies suggest that oestrogens have inhibitory effects on colon-cancer cells through oestrogen receptor β.

After examining all the evidence, the Working Group classified combined oral contraceptives as carcinogenic to humans (group 1). This conclusion was made on the basis of sufficient evidence of cervical cancer, breast cancer in present users and recent users, and liver cancer in populations with a low frequency of hepatitis-B infection. The Working Group stressed that there is also convincing evidence for a protective effect against endometrial cancer and ovarian cancer. This new assessment reaffirms the previous one[2] and extends it to include more cancer sites.

Because use of combined contraceptives heightens the risk of some cancers and reduces that of others, it is possible that the overall net public-health outcome could be beneficial, but a rigorous analysis is needed to show this. Such an analysis is outside the scope of an IARC monograph meeting and would include quantitative estimates of the age-specific absolute risk at each cancer site, the availability and effectiveness of cancer screening, the availability, effectiveness, and side-effects of cancer treatments, and other health and societal effects, both beneficial and adverse. Since these factors vary throughout the world, the risk-benefit analysis should be specific to each country and population.

Because people are living longer than in previous generations, there has been a quest to mitigate the effects of ageing. One approach has been to use hormonal treatment for women in menopause. Initial treatments included oestrogen only, but in 1975, a strong association was found with endometrial cancer. To reduce this risk, progestagens were added to the treatment, and use of this treatment rose again, especially in more developed countries. At its peak in around 2000, about 20 million women in more-developed countries were using combined hormone therapy, including half of all women in the USA who were aged 50–65 years. Use has been reduced by more than 50% since 2002, when clinical trials were halted after detecting an increased risk of breast cancer, coronary heart disease, and stroke.

Many epidemiological studies, including two large randomised trials, have investigated associations between use of combined hormone treatment and development of cancer at various sites. The studies consistently report a heightened risk of breast cancer in women who used combined hormone therapy. Mainly confined to present users or recent users, the risk increases with duration of use and exceeds that in women taking oestrogen-only treatment. Mechanistic data from randomised studies show that combined hormonal therapy causes a rise in cell proliferation in the postmenopausal human breast and substantially enhances the modest proliferation induced by oestrogen alone.

The risk of endometrial cancer depends on the number of days that progestagens are included in the combined treatment. When progestagens are taken for less than 10 days per month, the risk of endometrial cancer is significantly increased compared with that in never-users of this treatment. When progestagens are taken every day, the risk of endometrial cancer is much the same as that in never-users of hormonal treatment. By contrast with the findings for breast cancer, the increased risk of endometrial cancer in women taking combined treatment is much less than that in women taking oestrogen-only-therapy. The addition of progestagens prevents development of endometrial hyperplasia and reduces the rate of endometrial-cell proliferation caused by oestrogen-only treatment, as shown in randomised studies.

Several studies investigated an association with colorectal cancer, and the evidence suggests that combined hormone therapy does not heighten the risk of developing colorectal cancer. The few data available are inadequate to show whether combined hormone treatment alters the risk of cervical, ovarian, or liver cancer—three sites that are affected by combined contraceptives.

Receptor-mediated responses are a plausible mechanism for hormonal carcinogenesis, and research supports a direct genotoxic effect of hormones, hormone metabolites, or hormonal by-products such as reactive oxygen species. Both mechanisms could contribute to cancer formation. Cessation of hormonal treatment can reduce receptor-mediated effects, whereas genetic damage could be more persistent.

After examining all the evidence, the Working Group classified combined oestrogen-progestagen hormone therapy as carcinogenic to humans (group 1). This is a higher classification than before.[2] The Working Group did not find the evidence sufficient to infer a protective effect at any site.

Both beneficial and adverse effects other than cancer have been established for combined hormone therapy. As discussed before, a rigorous risk/benefit analysis would be of use to put the different effects in perspective, and assess the overall consequences for public health.

The contributors declare no conflicts of interest.

1 IARC monographs on the evaluation of carcinogenic risks to humans, volume 91, combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. Lyon: International Agency for Research on Cancer (in press).

2 IARC monographs on the evaluation of carcinogenic risks to humans, volume 72, hormonal contraception and post-menopausal hormonal therapy. Lyon: International Agency for Research on Cancer, 1999.

3 Cogliano V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F. Carcinogenicity of human papillomaviruses. *Lancet Oncol* 2005; **6**: 204.